## REMARKS

Claims 53-63, 67-70 and 72-86 are pending. Of these, claims 56 and 57 have been withdrawn from examination. Support for the preamble change in claim 53 is found generally in the application and, for example, at page 4, lines 9-29. Support for "antigen binding site" is found for example at page 10, lines 27-29 and page 34, lines 9-13. The new claims find support in the application and claims as originally filed. The amendments have been made to assist the Examiner to understand the claimed invention. The amendments have not been made to obviate prior art or overcome any rejection for patentability. The amendments raise no issue of new matter.

**Rejection under 35 U.S.C. §101 (Utility)**

The rejection of claims 53-55, 58-63 and 67-71 as reading on naturally occurring $C_H$BP in eukaryotic cells is respectfully traversed. The claimed array of eukaryotic cells is not naturally occurring because the cells are engineered to express the $C_H$BP. Thus, the rejection can be withdrawn.

**Rejection under 35 U.S.C. §112, First Paragraph (Written Description)**

The rejection of claims 53-55, 58-63 and 67-71 as allegedly failing to comply with the written description requirement is respectfully traversed. The Examiner has withdrawn the prior rejection for lack of a written description in view of the declaration of the declaration of Dr. Hiatt and Applicant's arguments. The withdrawn rejection was largely directed to the scope of $C_H$BP molecules that are encompassed in the claimed $C_H$BP array.

The Examiner now argues that "[n]one of the detail [sic] description describes a CHBP array in a eukaryotic cell having the stated properties of the IgBP." Office Action, page 4. The detailed description, as the Examiner asserts, "does not describe an array with polynucleotides encoding a protein that is at least 75% identity to a 25 consecutive amino acid portion of Ig light chain variable region etc" and the specification lacks "sufficient descriptive information, such as definitive structural for functional features of the array with the critical features of the encoded polypeptide." *Id.*

In sum, the Examiner's new position appears to be that although the specification provides a written description of the full genus of $C_HBP$ molecules of the claimed array, the specification fails to adequately describe the array. Applicants respectfully traverse the rejection.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35 U.S.C. § 112, first paragraph. *Id.* The USPTO's approach for evaluating the written description requirement as specified in *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement*, states that an adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1105 (2001) (emphasis added).

Prior to addressing the rejection, Applicants wish to point out that the claims are directed to an array of eukaryotic cells engineered to express a library of $C_HBP$. The library of different $C_HBP$ molecules is not within a single cell. Rather, the population of cells (or plants) which make up the cell array together represents the sum total of the library of different $C_HBP$ (i.e., different antigen binding molecules) of the array. Thus, Applicants take issue with statements in the rejection that characterize the invention as "a CHPB array in a eukaryotic cell." See e.g., Office Action, page 4, lines 12-14.

The Examiner's new position that there is inadequate description of the $C_HBP$ array is clearly untenable because the array is simply a population of cells that together expresses the various $C_HBP$ molecules of the array, which the Examiner has acknowledged is supported by a written description. Furthermore, the Examiner has failed to consider the various actual examples in the application which describe not one but a variety of eukaryotic cell $C_HBP$ arrays.

Example 1 of the application describes the cloning of heavy and light chain variable region genes from different donors of human bone marrow that contained B cells with antibodies to *Clostridium difficile* toxin A and B. Specification, page 44. The cDNA for the variable heavy and light chain genes is clearly polyclonal in nature because it was isolated from total bone marrow. See Specification, page 45, e.g., lines 26-30, emphasis added ("The amplified regions were then ligated into a vector to encode the heavy chain polynucleotide consisting of a signal sequence, *a diversity of variable region[s]* and the entire gamma constant region"). The Example describes insertion of the various heavy and light chain variable genes into a plant expression vector to produce "a recombinant population of vectors. *Id.* at page 46, 1st paragraph. Example 1 describes that transfection techniques were used to prepare "approximately 1,000 plants." *Id.* Such $C_HBP$ cell array was analyzed and found to represent a library of different $C_HBP$. *Id.* at page 47, second paragraph.

Example 2 describes a $C_HBP$ cell array prepared in eukaryotic (corn) cells using the heavy chain genes from Example 1 but with a hybrid constant region containing IgG and IgA sequence. Specification, page 49. Again, an array of approximately 1,000 corn plants were prepared and tested for antibodies to *Clostridium difficile* toxin A and B. 90 of the approximately 1,000 plants tested were determined to contain a $C_HBP$ cell with antigen binding. *Id.* at page 50.

Example 3 of the specification describes another $C_HBP$ cell array in corn which was prepared by sexually crossing the various antigen binding plants identified in the cell array from Example 2. In addition, Example 5 describes the preparation of a $C_HBP$ eukaryotic (insect) cell array where about 8% of the cell array were determined to be antigen binding. Still further, Example 6 describes the preparation of $C_HBP$ eukaryotic (mammalian/hamster) cell array where about 7% of the cell array were determined to be antigen binding.

Applicants submits that the above demonstrates that the Specification (using the Examples alone) provides more than adequate written description for the claimed eukaryotic cell array. Accordingly, reconsideration and withdrawal of the rejection is respectfully urged.

**Rejection for New Matter**

A new matter rejection is asserted for the language describing transfecting "**a population of eukaryotic cells with a library of at least two different $C_H$BP . . .** said library of at least two different $C_H$BP polynucleotides wherein each $C_H$BP polynucleotide encodes . . . ." Applicants assume that the Examiner is objecting to the bolded text within the quote, i.e., "a population of eukaryotic cells with a library of at least two different $C_H$BP," since this language was added during the previous response. This new matter rejection is respectfully traversed.

Support for the language at issue is clearly present in the claims as originally filed. Claim 1 as filed contains nearly identical language, shown with emphasis below.

> 1. A method for preparing an immunoglobulin binding protein *array* in plant cells, comprising the steps of: (a) **transforming a population of plant cells with a library of at least two different polynucleotides encoding different immunoglobulin binding protein (IgBP) polypeptides** that: (i) specifically bind to a ligand with a K.sub.D<10.sup.-6 moles/liter; or (ii) form one or more disulfide bonds with one or more polypeptides in the transfected cell, to generate a binding protein that specifically binds to a ligand with a K.sub.D<10.sup.-6 moles/liter; wherein the IgBP polypeptides (i) comprise four framework regions alternating with three complementarity determining regions and (ii) comprise at least one peptide sequence having at least 75% sequence identity to a framework region of a native IgM, IgG, IgA, IgD, IgE, IgY, kappa or lambda immunoglobulin molecule; and wherein the IgBP polypeptides are not detectably expressed by the plant cells prior to transformation; and (b) selecting transformed plant cells, and therefrom preparing an IgBP *array* in plant cells.

Additional support is found throughout the specification, the essence of which is to prepare arrays of Immunoglobulin binding protein (IgBP) polypeptides or arrays of components of IgBP, the latter including $C_H$BP. Specific support for these concepts is found for example at page 10, lines 8-24, which defines an IgBP as follows:

> Immunoglobulin binding protein (IgBP): An immunoglobulin binding protein (i) comprises an amino acid sequence that is at least 75% identical to at least one framework region of a native immunoglobulin molecule (e.g., IgM, IgG, IgA, IgD, IgE, IgY kappa or lambda) and (ii) is a functional binding protein.

> Framework regions are described below, under "Immunoglobulins." A protein P is a functional binding protein if (1) for one molecular, ionic or atomic ligand A the $K_D$ (P, A)<$10^{-6}$ moles/liter (preferably <$10^{-7}$ moles/liter), where $K_D$ (X,Y)=[X][Y]/[X:Y], and (2) for a different molecular, ionic or atomic species B, $K_D$ (P, B)>$10^{-4}$ moles/liter. Such a protein P is said to specifically bind A. Immunoglobulin binding proteins (IgBPs) generally function as a binding protein by virtue of the properties of a sequence of amino acids comprising a combining site, as defined below. An IgBP may comprise a single immunoglobulin chain or fragment thereof, multiple identical immunoglobulin chains or fragments thereof, or multiple non-identical immunoglobulin chains or fragments thereof. IgBPs include, for example, single chain antigen binding proteins, Fabs and Fvs. **Also included are heavy chain binding proteins ($C_H$BPs), discussed in greater detail below**.

As shown by emphasis added, the IgBP is a term that may also include $C_H$BP. In addition, the Specification at page 10 also defines an Ig component which is a polypeptide of an IgBP.

> Component of an IgBP: a polypeptide capable of forming one or more covalent bonds (preferably disulfide bonds) with one or more other polypeptides to generate a functional binding protein. A component is not itself a functional binding protein. For example, a multimeric antibody is considered an IgBP, and the polypeptide chains that are joined by covalent bonds to form an antigen binding site are considered to be IgBP components. Examples of such components include but are not limited to heavy chains and fragments thereof, light chains and fragments thereof, J chain and fragments thereof, and secretory component and fragments thereof.

The Specification starting at page 11, line 5, further defines a $C_H$BP as follows (emphasis added);

> Immunoglobulin heavy chain binding protein ($C_H$BP): **an IgBP** that (i) comprises multiple combining sites derived from (i.e., at least 75% identical to at least 25 consecutive amino acids of) either immunoglobulin light chain or heavy chain variable regions, but not both; and (ii) comprises a native heavy chain constant region sequence, or a fragment or other variant thereof, provided that the amino acid sequence of such a component is at least 75% identical to a constant region tailpiece (defined below) of a mu or alpha

> chain of a native immunoglobulin heavy chain. A $C_H$BP that comprises combining sites derived from one or more heavy chain variable regions does not comprise a combining site derived from a light chain variable region. Similarly, a $C_H$BP that comprises combining sites derived from one or more light chain variable regions does not comprise a combining site derived from a heavy chain variable region. Multiple $C_H$BP components may be covalently linked to generate a functional $C_H$BP, or a single polypeptide may be sufficient. Representative $C_H$BPs include proteins assembled from four alpha chains and one J chain, from twelve mu chains or from ten mu chains and at least on J chain.

Applicant wishes to point out that the definition of a $C_H$BP indicates that it is a form of a IgBP. In view of all the above definitions, one skilled in the art would understand that an IgBP includes a $C_H$BP which may be the sole polypeptide of the IgBP if the $C_H$BP exhibited the requisite binding activity, or that an IgBP may include a $C_H$BP and another immunoglobulin chain or fragment thereof which together with the $C_H$BP forms a functional binding site (e.g. a combining site formed by an Ig heavy and light chain).

Applicants further point out that the specification beginning at page 30 and extending to page 41 contains an extensive description of IgBP arrays and refers generally to IgBP or IgBP component arrays. As shown and discussed above, the term IgBP or IgBP component includes the term $C_H$BP. Furthermore, in one instance the specification directly alludes to makes $C_H$BP arrays. Specification, page 35, lines 3-4 (emphasis added) ("Within certain preferred embodiments, IgBP arrays (**preferably $C_H$BP arrays**) may be prepared in plants, plant cells and/or seeds."). As such one skilled in the art would understand that the discussion of IgBP arrays and IgBP component arrays includes arrays of $C_H$BPs.

Accordingly, as there is ample support for the language objected to, the new matter rejection may be withdrawn.

**Rejection under 35 U.S.C. §112, Second Paragraph**

The various rejections for alleged indefiniteness appear to result from a misunderstanding of the invention by the Examiner. Applicants have amended the preamble and body of claim 53

for better understanding and herein provide additional explanation of the invention. As such, Applicants respectfully submit that the various rejections are without basis and may be withdrawn.

**Rejection under 35 U.S.C. §103 (Obviousness)**

The rejection of claims 53-55, 58-63 and 67-71 as allegedly being obvious over Ma et al. (Eu J Immunol) or Hiatt et al. (Nature) in view of Dellaporta (USP 6569648). The Examiner notes that Ma or Hiatt disclose immunoglobulin expression in eukaryotic cells but acknowledges that these references fails to disclose an array of $C_H$BP in eukaryotic cells. Office Action, page 7. The Examiner turns to Dellaporta to provide the missing teaching. Applicants respectfully traverse the rejection.

In order to make a *prima facie* case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine (or modify) the teachings of the selected references, and (iii) provides a reasonable expectation of success. MPEP § 2143. This is the "TSM" test for obviousness which was recently affirmed by the Supreme Court. KSR Int'l Co. v. Teleflex Inc., No. 04-1350, 550 U.S. ____, slip op. at 15 (2007). In explicating the correct standard for this test, the KSR Court reaffirmed previous holdings that an invention "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." KSR, slip op. at 14.; see also, In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). Furthermore, the Court warned the factfinder to be aware of the distortion caused by hindsight bias and to be cautious of arguments reliant upon *ex post* reasoning. KSR, slip op. at 17.

The Examiner cites to column 3, line 40 to column 4, line 10 of Dellaporta for teaching that labeled gene specific probes that may be hybridized and detect directly on arrays, so as to screen large numbers of pools to identify insertional mutants. Office Action, page 7. Applicant points out that the cited text in Dellaporta describes the invention as an efficient method for selecting insertional mutations and offers a nucleic acid array on a solid support to identify any of a variety of insertional mutations from pools of nucleic acids. See, e.g., Dellaporta, column 2, lines 1-18. Applicants, however, are claiming a cell array, not a nucleic acid assay.

Applicants acknowledge, however, that Dellaporta describes making a population of cells each containing different insertional mutations. Dellaporta, column 3, lines 53-55. Dellaporta also contemplates mating different transgenic plants to produce offspring that contain multiple, "independently-segregating," insertion events. Dellaporta, paragraph bridging columns 8 and 9.

The instantly claimed cell array, however, differss in several respects from the population of insertional mutations described by Dellaporata. The claimed array of eukaryotic cells are engineered to express a library of $C_HBP$ result from expression in each cell of at least two different $C_HBP$ polynucleotides, each encoding an interacting set of polypeptides, e.g., a heavy and/or light chain of an immunoglobulin including a constant region tailpiece of a mu or alpha chain of a native immunoglobulin heavy chain (or variant). The design of these interacting polypeptides results in a molecule with at least four antigen binding sites having an affinity of $K_D<10^{-6}$ moles/liter for a ligand. In addition, the claimed array requires the cells of the array to express a different $C_HBP$.

In contrast, the mutations described by Dellaporta are insertional and thus designed to inactivate or significantly modify the function of an existing gene in the target cell. When multiple mutations are considered in a single cell or organism, Dellaporta does not contemplate any interaction. The only consideration given is that they be "independently-segregating." Dellaporta simply generates random insertion mutations in a genome and provides a solid phase DNA array for rapid screening.

Applicants respectfully submit that there is no motivation to combine the insertional mutation methods of Dellaporta with the expression of heterologous immunoglobulin genes in plants as described by the primary references. Dellaporta attempts to inactivate or significantly modify existing host genes in a cell by random insertions, while the primary references (Ma or Hiatt) describe transfection plant cells with heavy and light chain immunoglobulin genes to obtain antibodies from cells that do not naturally make antibodies. The two methods involve very different mutations and serve very different purposes (insertional mutation are used to discover gene function while antibody expression in plants is a protein production system). Applicants submit that Dellaporta's approach to make random mutations of existing genes

actually runs counter to that of Ma or Hiatt, which prepare plant cells that express an entirely foreign protein by inserting the genes encoding the heavy and light chain into the plant cell.

The rejection also lacks a reasonable expectation of success because the insertional mutations in Dellaporta are not even described. The main goal of Dellaporta is a nucleic acid screening assay that can identify any insertional mutation, even in pools containing different nucleic acid. The primary references only show that immunoglobulin chains can associate and form a binding site in a plant cell. The ability to make libraries of $C_HBP$ expressing cells result from expression in each cell of at least two different $C_HBP$ polynucleotides, each encoding an interacting set of polypeptides, e.g., a heavy and/or light chain of an immunoglobulin including a constant region tailpiece of a mu or alpha chain of a native immunoglobulin heavy chain (or variant) is not predicted from a combination of methods that use such disparate molecular approaches.

Reconsideration and withdrawal of the rejection is respectfully requested.

## CONCLUSION

Applicants believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Respectfully submitted,

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